Cochrane Library

Cochrane Database of Systematic Reviews

Lifestyle interventions for chronic gout (Review)

Moi JHY, Sriranganathan MK, Edwards CJ, Buchbinder R

Moi JHY, Sriranganathan MK, Edwards CJ, Buchbinder R.
Lifestyle interventions for chronic gout.
Cochrane Database of Systematic Reviews 2013, Issue 5. Art. No.: CD010039.
DOI: 10.1002/14651858.CD010039.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Lifestyle interventions for chronic gout

John HY Moi[1], Melonie K Sriranganathan[2], Christopher J Edwards[2], Rachelle Buchbinder[3]

[1]Department of Rheumatology, The Royal Melbourne Hospital, Parkville, Australia. [2]Department of Rheumatology, University Hospital Southampton NHS Foundation Trust, Southampton, UK. [3]Monash Department of Clinical Epidemiology, Cabrini Institute, Malvern, Australia

Contact: John HY Moi, Department of Rheumatology, The Royal Melbourne Hospital, Grattan Street, Parkville, Victoria, 3050, Australia. john.moi@mh.org.au.

Editorial group: Cochrane Musculoskeletal Group.
Publication status and date: Edited (no change to conclusions), published in Issue 9, 2019.

Citation: Moi JHY, Sriranganathan MK, Edwards CJ, Buchbinder R. Lifestyle interventions for chronic gout. *Cochrane Database of Systematic Reviews* 2013, Issue 5. Art. No.: CD010039. DOI: 10.1002/14651858.CD010039.pub2.

ABSTRACT

Background

Although lifestyle interventions are commonly recommended in the management of patients with chronic gout, the evidence from trial data for their benefits and safety has not been previously examined in a systematic review.

Objectives

The objective of this systematic review was to evaluate the benefits and safety of lifestyle interventions for the treatment of people with chronic gout.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE for studies on 5 April 2013. We also searched the 2010 to 2011 American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) abstracts and performed a handsearch of the reference lists of included articles.

Selection criteria

Studies were included if they were randomised or quasi-randomised controlled trials (RCTs or CCTs) which compared lifestyle interventions to another therapy (active or placebo) in patients with chronic gout. Outcomes of interest were changes in gout attack frequency, joint pain, serum urate levels, tophus size, function, quality of life and adverse effects.

Data collection and analysis

Two review authors independently applied methods recommended by The Cochrane Collaboration for the selection, appraisal, data collection and synthesis of studies. We assessed the quality of the body of evidence for each outcome using the GRADE approach.

Main results

Only one study (120 participants), at moderate risk of bias, was included in the review. Patients were randomised to one of three interventions: either skim milk powder (SMP) enriched with glycomacropeptide (GMP) and G600, non-enriched SMP or lactose powder, over a three-month period. The frequency of acute gout attacks, measured as the number of flares per month, decreased in all three groups over the three-month study period. Low quality evidence indicated that there was no difference between the SMP/GMP/G600 group and combined control groups (SMP and lactose powder) at three months (mean difference (MD) -0.21, 95% confidence interval (CI) -0.76 to 0.34). There were no significant between-group differences in terms of withdrawals due to adverse effects (risk ratio (RR) 1.27, 95% CI 0.53 to 3.03), and serious adverse events resulting in hospitalisation (2/40 SMP/GMP/G600 group versus 3/80 controls; RR 1.33, 95% CI 0.23 to 7.66). Gastrointestinal adverse effects were the most commonly reported. Pain from self reported gout flares, measured on a 10-point

Likert scale, improved more in the SMP/GMP/G600 group compared to controls (MD -1.03, 95% CI -1.96 to -0.10), an absolute difference of 10% (absolute risk difference -0.10, 95% CI -0.20 to -0.01). This is unlikely to be of clinical significance. There was no significant difference in physical function between SMP/GMP/G600 and the control groups at three-month followup (MD -0.03, 95% CI -0.14 to 0.08). Tophus regression and serum urate normalisation were not reported in this study.

Authors' conclusions

While there is good evidence from observational studies of an association between various lifestyle risk factors and gout development, there is a paucity of high-quality evidence from randomised controlled trials to either support or refute the use of lifestyle modifications for improving outcomes in people with chronic gout.

PLAIN LANGUAGE SUMMARY

Lifestyle interventions for chronic gout

This summary of a Cochrane review presents what we know from research about the effect of lifestyle modifications in the treatment of people with chronic gout. There was one study included in this review which looked at the benefits and safety of consuming skim milk powder (SMP) enriched with two components of dairy products (glycomacropeptide (GMP) and G600 milk fat extract) compared to standard skim milk or lactose powder in reducing the frequency of gout attacks over a three-month period.

The review shows that, in people with chronic gout:

Compared with standard skim milk or lactose powder, SMP enriched with GMP and G600 may not reduce the frequency of gout attacks, may not improve physical function, but may reduce pain. We do not know if consuming these dairy preparations improves tophus size (tophi are gout crystal deposits commonly found in skin, on the surface of joints or in cartilage) or blood uric acid levels, as these were not reported.

We do not have precise information about side effects and complications. Possible side effects may include nausea or diarrhoea.

What is gout and what are lifestyle interventions?

Gout is a very common form of painful joint inflammation (arthritis) caused by urate crystals forming either within or around joints. The inflammation can lead to pain, redness and swelling of affected joints, making the area difficult to touch or move. Some of the reasons why people get gout include their genetic makeup, being overweight, ingesting certain medications (e.g. diuretics), having impaired kidney function and lifestyle habits such as drinking excessive amounts of alcohol and sugar-sweetened drinks.

Although medications are the mainstay of gout treatment, given the recognised association between certain lifestyle risk factors and gout development, lifestyle changes such as losing weight, stopping smoking, exercising more, drinking more coffee and dairy products, and consuming less sugar-sweetened drinks, alcoholic beverages, meat and seafood are commonly recommended to people with chronic gout.

Best estimate of what happens to people with gout who consume enriched skim milk powder:

Gout attacks

People who consumed enriched skim milk powder had 0.21 fewer gout attacks per month at 3 months (or 2.5 fewer gout attacks per year) .

- People who consumed enriched skim milk powder had 0.49 gout attacks per month (or 6 gout attacks per year).

- People who consumed standard skim milk powder or lactose had 0.70 gout attacks per month (or 8 gout attacks per year).

Withdrawals due to adverse events

4 more people out of 100 who consumed enriched skim milk powder discontinued the supplement at 3 months (4% more withdrawals absolute change, from 10% fewer to 18% more).

- 18 out of 100 stopped consuming enriched skim milk powder.

- 14 out of 100 stopped consuming standard skim milk powder or lactose.

Pain (lower score means less pain)

People who consumed enriched skim milk powder rated their pain 1 point lower on a 0 to 10 point pain scale (10% absolute improvement; 20% to 1% improvement) at 3 months.

- People who consumed enriched skim milk powder rated their pain to be 0.67 points on a scale of 0 to 10.

- People who consumed standard skim milk powder or lactose rated their pain to be 1.7 points on a scale of 0 to 10.

Physical function (lower score means better function)

People who consumed enriched skim milk powder rated their function 0.03 better (0.14 better to 0.08 worse) on a 0 to 3 point scale (1% absolute improvement; 5% improvement to 3% worse) at 3 months.

- People who consumed enriched skim milk powder rated their function to be 0.08 points on a scale of 0 to 3.

- People who consumed standard skim milk powder or lactose rated their function to be 0.11 points on a scale of 0 to 3.

Serious adverse events

1 more person out of 100 who consumed enriched skim milk powder reported a serious adverse event.

- 5 out of 100 who consumed enriched skim milk powder had a serious adverse event.

- 4 out of 100 who consumed standard skim milk powder or lactose had a serious adverse event.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Skim milk enriched with GMP/G600 compared to skim milk & lactose powder for chronic gout

Skim milk enriched with GMP/G600 compared to skim milk & lactose powder for chronic gout

Patient or population: patients with chronic gout
Settings: outpatient, community
Intervention: Skim milk enriched with GMP/G600
Comparison: skim milk & lactose powder

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Skim milk & lactose powder	Skim milk enriched with GMP/G600				
Acute gout attack frequency participant self-report using gout flare diary Follow-up: 3 months	The mean acute gout attack frequency in the control groups was **0.6997 Number of gout flares per month**	The mean acute gout attack frequency in the intervention groups was **0.21 lower** (0.76 lower to 0.34 higher)		120 (1 study)	⊕⊕⊝⊝ **low**[1]	Not statistically significant[2]
Participant withdrawals due to adverse events participant and study investigator reported Follow-up: 3 months	**Study population**		**RR 1.27** (0.53 to 3.03)	120 (1 study)	⊕⊕⊝⊝ **low**[1]	Not statistically significant[3]
	138 per 1000	**175 per 1000** (73 to 417)				
	Moderate					
Joint pain reduction 10-point Likert scale (0 is no pain) Follow-up: 3 months	The mean joint pain reduction in the control groups was **-0.942**	The mean joint pain reduction in the intervention groups was **1.03 lower** (1.96 to 0.1 lower)		120 (1 study)	⊕⊕⊝⊝ **low**[1]	Absolute risk difference = -10% (-20% to -1%). Relative percentage change = -39% (-74% to -4%). NNTB = 10 (5 to 100)[2]
Tophus regression - not measured	See comment	See comment	Not estimable	-	See comment	Not measured

Physical function HAQ-II. Scale from: 0 to 3; 0 is minimal loss of function. Follow-up: 3 months	The mean physical function in the control groups was **0.11**	The mean physical function in the intervention groups was **0.03 lower** (0.14 lower to 0.08 higher)		120 (1 study)	⊕⊕⊖⊖ **low**[1]	Absolute risk difference = -1% (-5% to 3%). Relative percentage change = -13% (-58% to 33%) NNT n/a, not statistically significant[2]
Serum urate normalisation[4] - not reported	See comment	See comment	Not estimable[4]	-	See comment	Not reported
Serious adverse events participant and study investigator reported Follow-up: 3 months	**38 per 1000**	**50 per 1000** (9 to 287)	**RR 1.33** (0.23 to 7.66)	120 (1 study)	⊕⊕⊖⊖ **low**[1]	Gastrointestinal AEs (diarrhoea, nausea and flatulence) reported most commonly. SAE related to hospital admissions - none were due to the study products.[3]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] There was selective reporting of post-hoc comparisons between skim milk powder enriched with GMP/G600 and one of the two study controls (lactose) in relation to change in gout attack frequency from baseline
[2] Number needed to benefit (NNTB) = N/A when result is not statistically significant. NNT for continuous outcomes calculated using the Wells calculator software available from the CMSG editorial office.
[3] Number needed to harm (NNTH) = N/A when result is not statistically significant. NNT for dichotomous outcomes calculated using Cates NNT calculator (http://nntonline.net/ebm/visualrx/try.asp).
[4] Results only presented graphically

BACKGROUND

Description of the condition

Gout is a potentially progressive and debilitating form of chronic inflammatory arthritis, caused by deposition of monosodium urate crystals in synovial fluid and other tissues (Neogi 2011). It affects 1% to 2% of adults in developed countries (Richette 2010) and can have a significant adverse impact upon a person's quality of life. People who suffer from recurrent attacks frequently experience pain and disability, reduced health-related quality of life (HRQoL), reduced productivity and increased morbidity (Singh 2011a). Both its incidence and prevalence have appeared to rise in recent decades (Choi 2005a; Richette 2010). The reasons behind this are probably multi-factorial and potentially related to increasing longevity, rising rates of obesity and the metabolic syndrome, and shifts in dietary habits and lifestyle (Choi 2005a; Choi 2005b; Neogi 2011; Richette 2010).

Dietary risk factors that have been associated with the development of gout include increased dietary intake of purine-rich foods (particularly meat and seafood), ethanol (particular beer and spirits) and fructose-sweetened drinks (Choi 2004a; Choi 2004b; Neogi 2011; Singh 2011b). For this reason, lifestyle modifications are commonly co-prescribed in combination with urate-lowering medications (xanthine oxidase inhibitors, uricosuric agents, uricase agents) to help maintain monosodium urate levels below the serum saturation point (≤ 0.36 µmol/L or 6 mg/dL) to prevent crystal formation (Neogi 2011; Richette 2010). This has the aim of reducing hyperuricaemia and renal stone formation, promoting resolution of established crystal deposits, and decreasing the risk of recurrent gout flares and chronic arthropathy developing in the long term (Neogi 2011; Richette 2010).

Description of the intervention

Lifestyle interventions that may help in treating chronic gout include weight loss, smoking cessation, exercise, increased coffee and dairy intake, and dietary modification of fructose-sweetened drinks, alcoholic beverages, meat and seafood intake (either elimination or reduced intake).

How the intervention might work

Lifestyle interventions that involve reducing the dietary intake of purine-rich foods exert their effect by helping to lower the amount of purine precursors obtained from exogenous sources. Exogenous purine ultimately contributes to the total-body urate pool and predisposes to the development of hyperuricaemia and gout (Neogi 2011). Beer consumption is associated with increased plasma concentrations of urate precursors, hypoxanthine and xanthine (Dalbeth 2010). Furthermore, ethanol administration has been shown to have a hyperuricaemic effect by causing net adenosine triphosphate (ATP) degradation to adenosine diphosphate (ADP) and adenosine monophosphate (AMP), which can be rapidly degraded to uric acid (Choi 2005a). ATP is the molecule that supplies energy for cellular metabolism and is generated through the biochemical process known as oxidative phosphorylation (Fauci 2008). Fructose phosphorylation similarly consumes ATP in the liver and the accompanying catabolism of accumulated AMP results in increased uric acid production (Choi 2005a; Choi 2010). It is therefore anticipated that curtailment of meat, seafood, ethanol and fructose consumption would help in reducing hyperuricaemia and preventing chronic gout development.

Obesity and insulin resistance are both associated with the development of hyperuricaemia and the risk of incident gout in men. Obesity causes hyperuricaemia via increased urate production and decreased renal urate excretion (Choi 2005b). Insulin resistance is thought to impair oxidative phosphorylation, which, in turn, leads to increased levels of systemic adenosine and renal urate retention (Choi 2005a). Weight loss has been shown to reduce de novo purine synthesis. Both exercise and weight loss help to counteract the hyperuricaemic effects of obesity and insulin resistance.

The ingestion of milk proteins (casein, lactalbumin, orotic acid) has been shown to exert a uricosuric effect in healthy subjects. Soy and milk ingestion also promote renal oxypurine excretion, thereby reducing the availability of precursor substrates necessary for urate production (Choi 2004a; Dalbeth 2010). Coffee consumption helps reduce the risk of gout through several mechanisms. Caffeine (1,3,7-trimethyl xanthine) is a methyl xanthine and acts as a competitive inhibitor of xanthine oxidase. Mimicking the action of allopurinol, this impedes the endogenous synthesis of uric acid. Furthermore, caffeine promotes weight loss through stimulation of thermogenesis and energy expenditure. Higher long-term coffee intake also helps lower serum insulin levels and reduce insulin resistance (Choi 2007).

Why it is important to do this review

Despite the fact that lifestyle interventions are commonly recommended in the management of patients with recurrent gout, the evidence for their benefits and safety in clinical trials has not been previously examined in a systematic review. The results of this review are likely to be important for informing clinical practice and/or determining whether further research is required to establish the value of lifestyle interventions for gout.

OBJECTIVES

The objective of this systematic review was to evaluate the benefits and safety of lifestyle interventions for the treatment of people with chronic gout.

METHODS

Criteria for considering studies for this review

Types of studies

All published randomised or quasi-randomised controlled trials (RCTs or CCTs) which compared one or more lifestyle interventions to either no treatment, placebo, urate-lowering medications (uricases, uricosuric agents, xanthine oxidase inhibitors) or another lifestyle intervention for treating chronic gout were considered for inclusion. Studies of dietary supplements are covered in a separate Cochrane review and were excluded. Only trials that were published as full articles or were available as a full trial report were included.

Types of participants

Adult patients (aged 18 years or older) with diagnosed gout (author described or meets 1977 American College of Rheumatology

criteria for gout (Wallace 1977) or other criteria as specified in the study).

Types of interventions

All trials that evaluated one or a combination of lifestyle interventions were included. This included trials on weight loss, smoking cessation, exercise, increased coffee or dairy intake, and dietary modification (either elimination or reduced intake) of fructose-sweetened drinks, ethanol (particularly beer and spirits) and purine-rich foods (particularly meat and seafood).

Comparators could be:

1. placebo;
2. urate-lowering medications (uricases, uricosuric agents, xanthine oxidase inhibitors); or
3. other non-pharmacological interventions including lifestyle interventions used in treating gout.

Types of outcome measures

Main outcomes

1. Benefit: participant-reported reduction in acute gout attack frequency
2. Safety: number of study participant withdrawals due to adverse events (AEs)

Other outcomes

1. Joint pain reduction: mean change in pain score on a visual analogue scale (VAS) or numerical rating scale
2. Tophus regression
3. Physical function (i.e. activity limitation): as measured by disease-specific instruments (such as the Health Assessment Questionnaire Disability Index (HAQ-DI))
4. Health-related quality of life (HRQoL): as measured by generic instruments (such as the Medical Outcomes Study Short-Form-36 Survey (SF-36))
5. Serum urate (sUA) normalisation: sUA (Trinder Assay) reduction to < 0.36 mmol/L (6.1 mg/dL)
6. Serious adverse events (SAEs, defined as AEs that are fatal, life-threatening or require hospitalisation)
7. Patient global assessment via VAS

For the purpose of this review, if feasible, we planned to group trials into those of short-term (less than three months), medium-term (three to 12 months) and long-term (more than 12 months) duration.

We presented the following outcomes (at the latest time point) in a 'Summary of findings' tables (Schünemann 2011a; Schünemann 2011b): participant-reported reduction in acute gout attack frequency, number of study participant withdrawals due to AEs, joint pain reduction, physical function, patient global assessment, sUA normalisation and serious adverse events.

Search methods for identification of studies

Electronic searches

We searched the following databases for RCTs or CCTs using the search strategies detailed in the appendices:

1. Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, Issue 3, 2013) (Appendix 1);
2. MEDLINE Ovid (1948 to March week 3 2013) (Appendix 2);
3. EMBASE (1980 to week 13 2013) (Appendix 3).

We applied no language restrictions.

Searching other resources

We searched the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) conference abstracts from 2010 and 2011. We handsearched the reference lists of included articles and relevant reviews to identify any additional studies not retrieved by the aforementioned search strategy.

Data collection and analysis

Selection of studies

Two review authors (JM, MS) independently assessed all retrieved trials to identify those that fulfilled the criteria for inclusion in this systematic review. We retrieved all relevant articles in full text for closer examination. Disagreements about study inclusion or exclusion were resolved by consensus or by discussion with a third author (RB) if needed. We planned to translate studies into English where necessary.

Data extraction and management

Two authors (JM, MS) independently extracted the following relevant information from included trials using a pre-defined data extraction form: study design, characteristics of the study population (age, gender, presence or absence of concurrent urate-lowering medication use or tophi), lifestyle interventions, control interventions, outcome measures (mean and standard deviation for continuous outcomes, number of events and participants for dichotomous outcomes), timing of outcome assessment and methodological domains relevant to 'Risk of bias' assessment. We resolved differences in data extraction by referring back to the original articles and establishing consensus. A third author (RB) was consulted to help resolve differences.

Assessment of risk of bias in included studies

We assessed the potential for bias in the included studies using The Cochrane Collaboration's tool for assessing risk of bias (Higgins 2011). Two review authors (JM, MS) independently assessed the risk of bias in included trials and resolved any disagreements by consensus or consultation with a third author (RB). We assessed the following methodological domains:

1. random sequence generation: to determine if the method of generating the randomisation sequence was adequate to prevent biased allocation to interventions;
2. allocation concealment: to determine if adequate methods were used to conceal allocation to interventions;
3. blinding of participants, personnel and outcome assessors for each outcome measure: to determine if adequate methods to prevent knowledge of the allocated interventions by study participants, personnel and outcome assessors occurred during the study;
4. incomplete outcome data;
5. selective outcome reporting; and
6. other potential sources of bias.

To determine the risk of bias of an included study, for each criterion we evaluated the presence of sufficient information and the likelihood of potential bias. We rated each of these criteria either as 'low risk', 'high risk' or 'unclear risk' (either lack of information or uncertainty over the potential for bias).

Measures of treatment effect

We planned to summarise the data in a meta-analysis only if there was sufficient clinical and statistical homogeneity. For continuous data, we analysed results as mean differences (MDs) between the intervention and comparator group, with corresponding 95% confidence intervals (CIs). For MDs between intervention and control groups, we planned to weight these by the inverse of the variance in the pooled treatment estimate. However, when different scales were used to measure the same conceptual outcome (e.g. function or pain), we planned to calculate standardised mean differences (SMDs) instead, with corresponding 95% CIs. SMDs are calculated by dividing the MD by the standard deviation, resulting in a unitless measure of treatment effect. For dichotomous data, we calculated a risk ratio (RR) with corresponding 95% CI.

Unit of analysis issues

For studies containing more than two intervention groups, making multiple pair-wise comparisons between all possible pairs of intervention groups possible, we planned to include the same group of participants only once in the meta-analysis. In the event that cross-over trials were identified in which the reporting of continuous outcome data precluded paired analysis, we planned to include these data in a meta-analysis, in order to avoid unit of analysis error. Where carry-over effects were thought to exist, and where sufficient data existed, we would include data from the first period only in the analysis (Higgins 2011). Where outcomes were collected at multiple follow-up times (within the short-term, medium-term and long-term time frames), we extracted the last outcome.

Dealing with missing data

Where data were missing or incomplete, we sought further information from the study authors. In cases where individuals were missing from the reported results and no further information was forthcoming from the study authors, we assumed the missing values had a poor outcome.

For dichotomous outcomes that measured adverse events (e.g. number of withdrawals due to adverse events), we calculated the withdrawal rate using the number of patients that received treatment as the denominator (worst-case analysis). For dichotomous outcomes that measured benefits (e.g. patient-reported reduction in gout attack frequency), we calculated the worst-case analysis using the number of randomised subjects as the denominator.

For continuous outcomes (e.g. pain), we calculated the MD or SMD based on the number of patients analysed at the time point. If the number of patients analysed was not presented for each time point, we used the number of randomised patients in each group at baseline. Where possible, we computed missing standard deviations from other statistics such as standard errors, confidence intervals or P values, according to the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If standard deviations could not be calculated, they were to be imputed (e.g. from other studies in the meta-analysis; Higgins 2011).

Assessment of heterogeneity

Prior to planned meta-analysis, we assessed studies for clinical homogeneity with respect to type of therapy, control group and the outcomes. For any studies judged as clinically homogeneous, we planned to estimate statistical heterogeneity using the I^2 statistic (Deeks 2011), using the following as a rough guide for interpretation: 0% to 40% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity and 75% to 100% considerable heterogeneity. In cases of considerable heterogeneity (defined as $I^2 \geq 75\%$), we planned to explore the data further, including subgroup analysis, in an attempt to explain the heterogeneity.

Assessment of reporting biases

In order to determine whether reporting bias was present, we determined whether the protocol for the RCT was published before recruitment of study patients was started. For studies published after 1 July 2005, we screened the Clinical Trial Register at the International Clinical Trials Registry Platform of the World Health Organization (http://apps.who.int/trialsearch/) (DeAngelis 2004).

We evaluated whether selective reporting of outcomes was present (outcome reporting bias).

We compared the fixed-effect estimate against the random-effects model to assess the possible presence of small sample bias in the published literature (i.e. in which the intervention effect was more beneficial in smaller studies). In the presence of small sample bias, the random-effects estimate of the intervention is more beneficial than the fixed-effect estimate (Sterne 2011). We planned to further explore the potential for reporting bias with funnel plots if more than 10 studies were included.

Data synthesis

Where studies were sufficiently homogeneous that it was clinically meaningful for them to be pooled, we planned to perform meta-analysis using a random-effects model, regardless of the I^2 results. We performed analysis using The Cochrane Collaboration's statistical software Review Manager 2011 and produced forest plots.

Subgroup analysis and investigation of heterogeneity

Where sufficient data were available, we planned to perform the following subgroup analyses:

1. men versus postmenopausal women;
2. presence or absence of concurrent urate-lowering medication use; and
3. presence or absence of tophi.

Thus, ideally we would have liked to extract the main outcome for the above subgroups within each trial (e.g. men versus women). We considered each of the three planned subgroup analyses separately. We planned to informally compare the magnitudes of effect to assess possible differences in response to treatment between the subgroups. We planned to assess the overlap of the confidence intervals; non-overlap of the confidence intervals

indicated statistically significant differences between subgroups. However, we anticipated that the outcomes may not be reported by subgroups within the trials, precluding the planned analyses.

Sensitivity analysis

If sufficient studies existed, we planned sensitivity analyses to assess the impact of any bias attributable to inadequate or unclear treatment allocation (including studies with quasi-randomised designs) and inadequate blinding of study participants, personnel and outcome assessors.

Presentation of key results

We produced a 'Summary of findings' table to illustrate key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the most important patient-relevant outcomes, as recommended by The Cochrane Collaboration (Schünemann 2011a). The outcomes that were included in the 'Summary of findings' table included participant-reported reduction in acute gout attack frequency, number of study participant withdrawals due to AEs, joint pain reduction, function, tophus regression, serum urate normalisation and serious adverse events.

The 'Summary of findings' table included an overall grading of the evidence related to each of the main outcomes using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (Schünemann 2011b). In addition to the absolute and relative magnitude of effect provided in the 'Summary of findings' table, for dichotomous outcomes we calculated the number needed to treat to benefit (NNTB) or the number needed to treat to harm (NNTH) from the control group event rate (unless the population event rate was known) and the risk ratio using the 'Visual Rx' programme (Cates 2008). For continuous outcomes, we calculated the NNT using the Wells calculator software available at the Cochrane Musculoskeletal Group editorial office. We determined the minimal clinically important difference (MCID) for each outcome for input into the calculator.

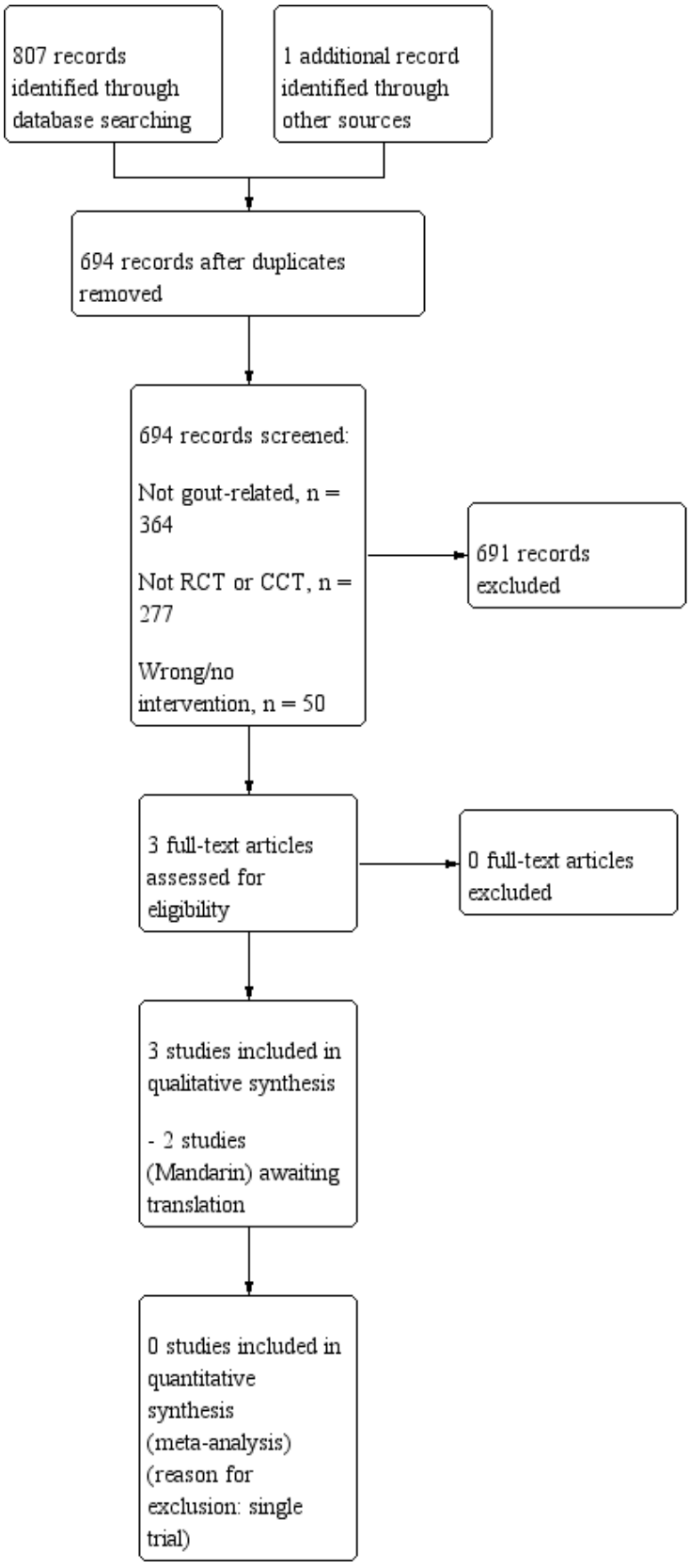
RESULTS

Description of studies

Results of the search

The search strategy yielded 808 references (see Figure 1). After excluding 114 duplicate references, 277 references that were not RCTs or CCTs, 364 non-gout related references and 50 references with no or incorrect interventions, we retrieved three articles for full assessment. Only one study published in English was found to meet our inclusion criteria (Dalbeth 2012). Two other trials were published in Mandarin and are awaiting translation and classification (Zeng 2012; Zhao 2009). The review will be updated to include data from these studies if they are found to meet the inclusion criteria.

Figure 1. Study flow diagram.



Included studies

Details of the included trial are provided in the table 'Characteristics of included studies'. The RCT was performed in New Zealand, was of parallel-group design, included 120 participants and was of three months duration (Dalbeth 2012).

Study participants

Dalbeth 2012 included participants with chronic gout who met the American College of Rheumatology's diagnostic classification for gout. Participants were predominantly middle-aged Caucasian men (mean age in the fifth decade), duration of gout ranged from 13 to 17 years, and 20% to 43% of participants had tophaceous disease. Participants experienced frequent gout flares (defined as at least two flares in the preceding four months) at the time of study enrolment. Renal function was normal in participants (mean serum creatinine 91 µmol/l) and serum urate levels ranged from 0.41 to 0.44 mmol/l. The proportion of patients receiving background non-steroidal anti-inflammatory drugs (NSAIDs) was 25% to 28%, colchicine (range 18% to 33%), prednisolone (range 10% to 20%) and diuretics (2.5% to 20%). Participants continued their stable background allopurinol therapy for the duration of the study.

Interventions

Dalbeth 2012 compared two 'active control' dairy products (lactose powder 15 grams per day and skim milk powder (SMP) 15 grams per day) to SMP enriched with dairy fractions glycomacropeptide (GMP) 1.5 grams per day and 0.525 grams per day of G600 milk fat extract (SMP/GMP/G600), over a three-month period. GMP and G600 have been shown to have anti-inflammatory properties in experimental models of acute gout (Dalbeth 2012).

Timing of follow-up

Dalbeth 2012 reported outcomes at one, two and three months after exposure to the dairy interventions.

Outcome assessment

Dalbeth 2012 reported five of the seven essential outcome domains proposed by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) network for use in studies of chronic gout (Schumacher 2009). These study endpoints include reduction in gout attack frequency (measured using a participant-maintained daily gout flare diary), joint pain (measured with a 10-point Likert scale and by recording medication usage for treating gout attacks), participant global assessment (100 mm VAS), physical function (measured using the health assessment questionnaire (HAQ-II)) and serum urate level.

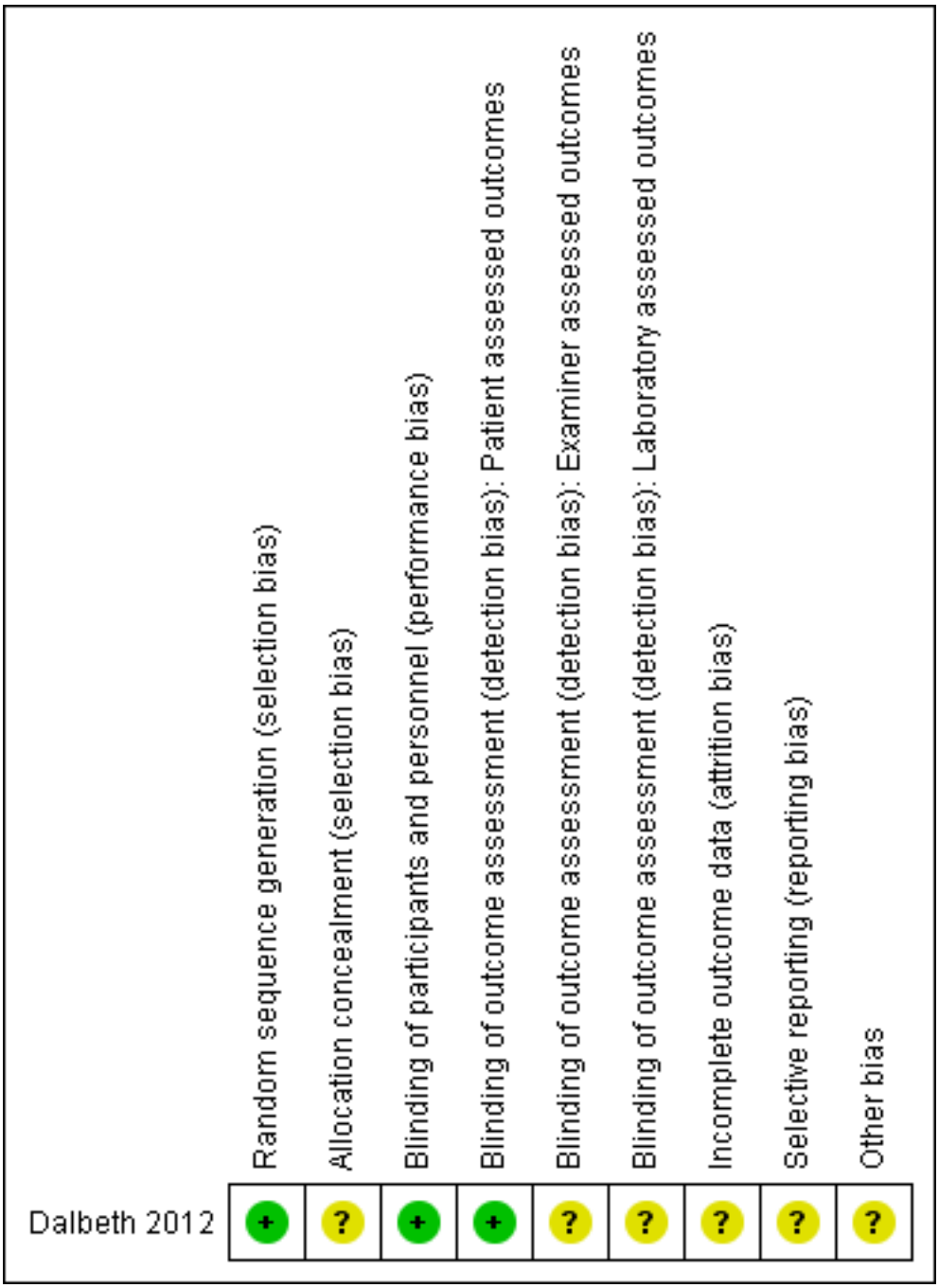
Excluded studies

No studies were excluded after review of the full text of potentially eligible articles.

Risk of bias in included studies

The results of the 'Risk of bias' assessment are presented in Figure 2. The included trial failed to meet all of the criteria for low risk of bias and the results may therefore be biased.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Dalbeth 2012 adequately described their method of random sequence generation as involving the use of a random block randomisation algorithm. However, insufficient details were provided to confirm allocation concealment to study interventions.

Blinding

Dalbeth 2012 reported blinding of both participants and study personnel to treatment allocation throughout the study. The primary study endpoint was based on patient self report (i.e. change in gout attack frequency, recorded using a participant-maintained daily gout flare diary). Outcome assessor blinding was only relevant to the assessment of secondary outcome measures including physical examination, evaluation of laboratory tests and enquiry regarding adverse events.

Incomplete outcome data

Dalbeth 2012 reported a 15% study participant drop-out rate, with the distribution of losses across treatment groups not specified. This study's risk of attrition bias was unclear.

Selective reporting

Dalbeth 2012 reported the data for all pre-specified outcomes. However, Dalbeth 2012 also reported the findings of a post hoc comparison between two interventions (SMP enriched with GMP and G600, lactose control) and their effects on the study's primary endpoint (change in gout flare frequency), although not the results of the third intervention (standard SMP). The same selective reporting occurred in the study authors' discussion of SMP/GMP/G600's effect on lowering diastolic blood pressure, only reporting the results of its post hoc comparison with the lactose control group.

Other potential sources of bias

Three of the study authors were employed by one of the organisations which helped to fund the study, while three other study authors were named inventors on a patent application related to milk products and gout. Given the declared conflicts of interest, the potential for bias could not be excluded.

Effects of interventions

See: **Summary of findings for the main comparison** Skim milk enriched with GMP/G600 compared to skim milk & lactose powder for chronic gout

See: Summary of findings table 1 for the main comparison. A meta-analysis was not performed as there was only one included trial.

Skim milk enriched with GMP and G600 versus skim milk and lactose powder

One trial (120 participants) indicated that all three dairy preparations, skim milk powder (SMP) enriched with glycomacropeptide (GMP) and G600, standard SMP and lactose powder, significantly reduced the frequency of gout flares over a three-month study period (Dalbeth 2012). After combining the two control groups (standard SMP, lactose powder) and calculating the standard deviation (SD) from the 95% confidence interval, we found no statistical difference between SMP/GMP/G600 compared to the two control groups in terms of the change in the number of gout flares from baseline: mean difference (MD) -0.21 (95% confidence interval (CI) -0.76 to 0.34) (Analysis 1.1, Figure 3). There was also no between-group difference in function (Analysis 1.2, Figure 4).

Figure 3. Forest plot of comparison: 1 SMP (GMP/G600) versus control (SMP/lactose), outcome: 1.1 Number of gout flares per month, after 3 months SMP (GMP/G600) versus control (SMP/lactose).

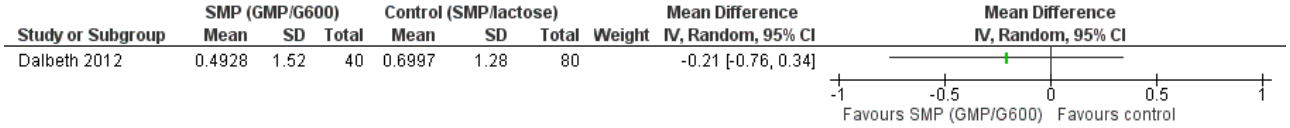
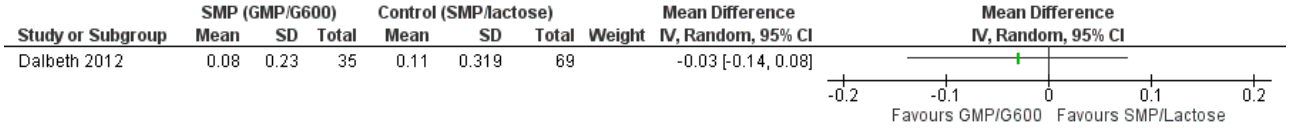


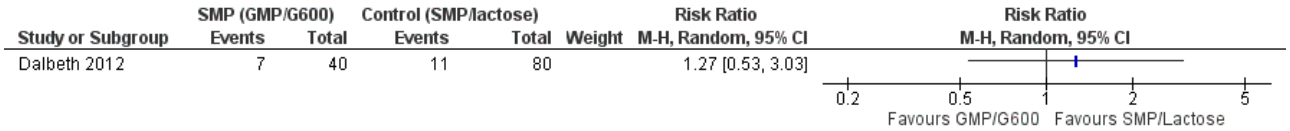
Figure 4. Forest plot of comparison: 1 SMP (GMP/G600) versus control (SMP/lactose), outcome: 1.2 Physical Function.



For the other efficacy outcomes included in this review, we found a statistical difference between SMP/GMP/G600 and the two control groups in change in pain from self reported gout flares (MD -1.03, 95% CI -1.96 to -0.10) and reduction in tender joint count from baseline (MD -0.49, 95% CI -0.85 to -0.12). A change of one point on a 10-point Likert scale may be a clinically meaningful result, given Khanna 2011 have previously reported this to be the minimally important difference (MID) for pain reduction in a randomised controlled trial (RCT) of rilonacept for preventing gout flares during initiation of allopurinol therapy. MID or minimally clinically important difference (MCID) is defined as the smallest difference in score in the domain of interest that patients perceive as beneficial (or worse) and that may lead to, in the absence of troublesome side effects and excessive costs, a change in the patient's management (Khanna 2011). The clinical significance of a reduction in tender joint count by half a joint over a three-month period is less clear, however, though it might possibly benefit patients who experience recurrent monoarticular (as opposed to polyarticular) attacks of acute gout. No statistical difference between groups was detected for change in swollen joint count from baseline (MD -0.23, 95% CI -0.61 to 0.16) and reduction in the number of self reported flares (MD -0.49, 95% CI -1.08 to 0.09).

The trial authors reported similar adverse event (AE) and discontinuation rates between the three study groups. We similarly found no differences between SMP/GMP/G600 compared to the two control groups in terms of withdrawals due to AEs (7/40 SMP/GMP/G600 group versus 11/80 control groups; risk ratio (RR) 1.27, 95% CI 0.53 to 3.03) (Analysis 1.3, Figure 5), number of participants reporting AEs (RR 0.97, 95% CI 0.66 to 1.45) and number of participants reporting serious adverse events (SAEs) (2/40 SMP/GMP/G600 group versus 3/80 control groups; RR 1.33, 95% CI 0.23 to 7.66).

Figure 5. Forest plot of comparison: 1 SMP (GMP/G600) versus control (SMP/lactose), outcome: 1.3 Participant withdrawals due to adverse events.



The trial authors reported no statistical difference with the intake of SMP/GMP/G600 in terms of changes in serum creatinine, serum urate concentrations, C-reactive protein levels, waist circumference, serum lipid profile or weight over time compared with standard SMP and lactose controls. Diastolic blood pressure was reported by the trial authors to decrease by a mean of 3.6 mmHg (95% CI ± 1.8) in the SMP/GMP/G600 group over the study period (P = 0.0002), with a greater reduction in diastolic blood pressure recorded when compared with the lactose control (Tukey post hoc test, P = 0.001).

DISCUSSION

Summary of main results

Only one trial evaluating skim milk enriched with glycomacropeptide (GMP) and G600 for chronic gout was identified. This trial of 120 participants, at moderate risk of bias, compared skim milk enriched with GMP and G600 to standard skim milk and lactose powder controls and found a small reduction in the frequency of gout flares (their primary measure of treatment benefit) in all three treatment groups over a three-month study period, with no significant between-group differences. Small reductions in self reported pain from gout flares and a reduction in tender joint count from baseline were also reported, while no differences were seen in physical function, swollen joint count, serum urate and C-reactive protein levels. There was no evidence of an increase in withdrawals due to adverse events or adverse events in participants in the SMP/GMP/G600 group compared to controls, with gastrointestinal adverse effects cited as the most common complaint in both groups.

Compared to standard skim milk or lactose powder, skim milk enriched with GMP and G600 is of unclear benefit in reducing flares of gout based on a single trial that is at moderate risk of bias.

Overall completeness and applicability of evidence

There was a notable lack of trial data to support commonly prescribed lifestyle interventions used in both primary and secondary prevention of gout. Despite evidence from cross-sectional observational studies of a harmful association between the consumption of alcohol (beer, liquor), fructose, sugar-sweetened soft drinks, sweet fruits (apples, oranges), meat, seafood (oily fish, shellfish) and gout development, and the reported protective effects of decaffeinated coffee and vitamin C intake (Choi 2010), there was no trial evidence to support these observations.

Quality of the evidence

Overall we judged the included trial (120 participants) to be at moderate overall risk of bias in view of the fact that we assessed four out of the seven domains of 'Risk of bias' assessment as unclear, with particular concern raised regarding selective reporting bias of post hoc comparison results. We suspect that the small number of trials identified is likely to be a reflection of a lack of high-quality research in the area rather than publication bias.

Potential biases in the review process

We are confident that the broad literature search used in this review has captured relevant literature and minimised the likelihood that we missed any relevant trials. In the event of incomplete or unclear reporting of trial data, we contacted the trial authors to obtain pertinent unpublished data and sought clarification of results, respectively. In the case of eligible trials being published in languages other than English, we requested translation of trials. Two authors undertook trial selection, data extraction and 'Risk of bias' assessment independently to minimise bias.

Agreements and disagreements with other studies or reviews

The findings of our review are, in part, consistent with the conclusions of a recent paper which aimed to provide recommendations on the use of lifestyle and dietary modifications for the management of gout, while considering the potential health benefits and risks of adopting these changes on comorbidities (e.g. the metabolic syndrome) which frequently co-exist in the same patients (Choi 2010). One of the recommendations of this review was to drink skim milk or other low-fat dairy products (up to two servings daily), given their reported benefits in lowering serum uric acid levels (Choi 2004a; Choi 2005c) and reducing the incidence of coronary heart disease (Hu 1999), premenopausal breast cancer (Shin 2002), colon cancer (Kampman 2000) and type 2 diabetes in observational studies (Choi 2005d). We found one trial, at moderate risk of bias, which showed that skim milk had similar effects to consuming lactose powder or skim milk enriched with GMP and G600 on the frequency of gout flares.

While the other lifestyle and dietary modifications advised are likely to be beneficial in the management of comorbid cardiovascular disease and the metabolic syndrome, their role in gout management currently remains unproven, due to the lack of evidence from high-quality trials.

AUTHORS' CONCLUSIONS

Implications for practice

While there is good evidence from observational studies of an association between various lifestyle risk factors and the development of gout, there is a paucity of high-quality evidence to either support or refute the use of lifestyle interventions for treatment of chronic gout. There is a single trial, at moderate risk of bias, which shows that skim milk enriched with GMP and G600 provides no added benefit over standard skim milk or lactose powder in reducing the frequency of gout flares in people with chronic gout.

Implications for research

Randomised controlled trials comparing lifestyle interventions to placebo, no treatment, other lifestyle interventions and urate-lowering medications are needed before any conclusions can be made about the role of lifestyle interventions for reducing gout attack frequency in people with chronic gout. However, we acknowledge that short-term trials may not be the optimal method for assessing the benefits and long-term sustainability of lifestyle modifications and long-term prospective longitudinal studies or registry data may also be required.

Planned trials should include participants with a range of gout manifestations (e.g. tophi, nephrolithiasis), co-morbidities that influence pharmacotherapy choice for gout treatment (e.g. renal impairment, cardiovascular disease) and assess outcomes recommended by OMERACT for studies of chronic gout, including reduction in gout attack frequency, joint pain, serum urate concentration, tophus burden, physical function and quality of life (Singh 2011a). The CONSORT statement should also be used as a guide for both designing and reporting trials (Boutron 2008).

Trial reporting should include the method of randomisation and treatment allocation concealment, blinding of study participants, study personnel and outcome assessment, follow-up of all participants who entered the trial and complete reporting of outcomes. Sample sizes should be reported and have adequate power to answer the research question; ideally trials should assess both the benefits and risks of lifestyle interventions. To enable comparison and pooling of the results of randomised controlled trials, we suggest that future trials report means with standard deviations for continuous measures or number of events and total numbers analysed for dichotomous measures, and use standardised measurement tools for reporting relevant outcomes.

ACKNOWLEDGEMENTS

The authors thank Louise Falzon, former Trials Search Co-ordinator of the Cochrane Musculoskeletal Group, for assisting with the design of the search strategy, and trial author Nicola Dalbeth, for providing unpublished HAQ outcome data.

REFERENCES

References to studies included in this review

Dalbeth 2012 *{published and unpublished data}*

* Dalbeth N, Ames R, Gamble GD, Horne A, Wong S, Kuhn-Sherlock B, et al. Effects of skim milk powder enriched with glycomacropeptide and G600 milk fat extract on frequency of gout flares: a proof-of-concept randomised controlled trial. *Annals of the Rheumatic Diseases* 2012;**71**:929–34.

References to studies awaiting assessment

Zeng 2012 *{published data only}*

Zeng, Y. C.Huang, S. F.Mu, G. P.Wang, T. F. Effects of adjusted proportional macronutrient intake on serum uric acid, blood lipids, renal function, and outcome of patients with gout and overweight. *Chinese Journal of Clinical Nutrition* 2012;**20**(4):210-4.

Zhao 2009 *{published data only}*

Zhao, Q. W.Liu, J.Qu, X. D.Li, W.Wang, S.Gao, Y.Zhu, L. W. Observation on therapeutic effect of electroacupuncture plus blood-letting puncture and cupping combined with diet intervention for treatment of acute gouty arthritis. *Zhongguo zhen jiu [Chinese Acupuncture & Moxibustion]* 2009;**29**(9):711-3.

Additional references

Boutron 2008

Boutron I, Moher D, Altman DG, Schulz K, Ravaud P, for the CONSORT group. Methods and processes of the CONSORT Group: example of an extension for trials assessing nonpharmacologic treatments. *Annals of Internal Medicine* 2008;**148**:295–309.

Cates 2008 [Computer program]

Dr Christopher Cates. Dr Chris Cates' EBM website, Visual Rx. Version 3. Dr Christopher Cates, 2008.

Choi 2004a

Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Purine-rich foods, dairy and protein intake, and the risk of gout in men. *New England Journal of Medicine* 2004;**350**:1093-103.

Choi 2004b

Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Alcohol intake and risk of incident gout in men: a prospective study. *Lancet* 2004;**363**:1277-81.

Choi 2005a

Choi KY, Mount DB, Reginato AM. Pathogenesis of gout. *Annals of Internal Medicine* 2005;**143**(7):499-516.

Choi 2005b

Choi HK, Atkinson K, Karlson EW, Curhan G. Obesity, weight change, hypertension, diuretic use, and risk of gout in men. *Archives of Internal Medicine* 2005;**165**:742-8.

Choi 2005c

Choi HK, Liu S, Curhan G. Intake of purine-rich foods, protein, dairy products, and serum uric acid level: the Third National Health and Nutrition Examination Survey. *Arthritis and Rheumatism* 2005;**52**:283–9.

Choi 2005d

Choi HK, Willett WC, Stampfer M, Rimm E, Hu FB. Dairy consumption and risk of type 2 diabetes mellitus in men: a prospective study. *Archives of Internal Medicine* 2005;**165**:997-1003.

Choi 2007

Choi HK, Willett W, Curhan G. Coffee consumption and risk of incident gout in men. *Arthritis and Rheumatism* 2007;**56**(6):2049-55.

Choi 2010

Choi HK, Willett W, Curhan G. Fructose-rich beverages and risk of gout in women. *JAMA* 2010;**304**(20):2270-8.

Dalbeth 2010

Dalbeth N, Wong S, Gamble GD, Horne A, Mason B, Pool B, et al. Acute effect of milk on serum urate concentrations: a randomised controlled crossover trial. *Annals of the Rheumatic Diseases* 2010;**69**:1677-82.

DeAngelis 2004

DeAngelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *JAMA* 2004;**292**:1363-4.

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Fauci 2008

Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, et al. Harrison's Principles of Internal Medicine. 17th Edition. McGraw Hill, 2008:2690.

Higgins 2011

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing the risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hu 1999

Hu FB, Stampfer MJ, Manson JE, Ascherio A, Colditz GA, Speizer FE, et al. Dietary saturated fats and their food sources in relation to the risk of coronary heart disease in women. *American Journal of Clinical Nutrition* 1999;**70**:1001–8.

Kampman 2000

Kampman E, Slattery ML, Caan B, Potter JD. Calcium, vitamin D, sunshine exposure, dairy products and colon cancer risk (United States). *Cancer Causes and Control* 2000;**11**:459-66.

Khanna 2011

Khanna D, Sarkin AJ, Khanna PP, Shieh MM, Kavanaugh AF, Terkeltaub RA, et al. Minimally important differences of the gout impact scale in a randomized controlled trial. *Rheumatology (Oxford)* 2011;**50**:1331-6.

Neogi 2011

Neogi T. Gout. *New England Journal of Medicine* 2011;**364**:443-52.

Review Manager 2011 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

Richette 2010

Richette P, Bardin T. Gout. *Lancet* 2010;**375**:318-28.

Schumacher 2009

Schumacher HR, Taylor W, Edwards L, Grainger R, Schlesinger N, Dalbeth N, et al. Outcome domains for studies of acute and chronic gout. *Journal of Rheumatology* 2009;**36**:2342–5.

Schünemann 2011a

Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Schünemann 2011b

Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Shin 2002

Shin MH, Holmes MD, Hankinson SE, Wu K, Colditz GA, Willett WC. Intake of dairy products, calcium, and vitamin D and risk of breast cancer. *Journal of the National Cancer Institute* 2002;**94**:1301-11.

Singh 2011a

Singh JA, Taylor WJ, Simon LS, Khanna PP, Stamp LK, McQueen FM, et al. Patient-reported outcomes in chronic gout: a report from OMERACT 10. *Journal of Rheumatology* 2011;**38**:1452-7.

Singh 2011b

Singh JA, Reddy SG, Kundukulam J. Risk factors for gout and prevention: a systematic review of the literature. *Current Opinion in Rheumatology* 2011;**23**:192-202.

Sterne 2011

Sterne JAC, Egger M, Moher D (editors). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Intervention* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Wallace 1977

Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yü T-F. Preliminary criteria for the classification of the acute arthritis of primary gout. *Arthritis and Rheumatism* 1977;**20**:895-900.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Dalbeth 2012

Methods	Randomised, double blind, 3-arm, parallel-group, controlled trial
	Duration: 3 months
	Withdrawals: 18 (distribution of losses not known despite attempts to contact the study author)
	Pre-specified sample size calculation: reported
	Intention-to-treat analysis: performed
Participants	N = 120
	Inclusion criteria:
	1. Adults aged ≥ 18 years

Dalbeth 2012 *(Continued)*

2. Gout diagnosed (according to the American College of Rheumatology diagnostic classification, recurrent gout flares (at least 2 flares in the preceding 4 months)

3. Participants experiencing frequent gout flares at the time of study enrolment (≥ 2 flares in the preceding 4 months)

Exclusion criteria:

1. Lactose intolerance
2. Severe renal impairment (defined as estimated glomerular filtration rate (eGFR) < 30 ml/min)

Lactose group (n = 40):

1. Males, n (%): 37 (93)

2. Mean age, years (SD): 57 (16)

3. Caucasian ethnicity, n (%): 28 (70)

4. Number of self reported flares in preceding 4 months, mean (SD): 3.9 (2.7)

5. Number of gout flares in baseline month, mean (SD): 1.3 (1.5)

6. Allopurinol use, n (%): 21 (53)

7. Colchicine use, n (%): 12 (30)

8. Prednisone use, n (%): 4 (10)

9. NSAID use, n (%): 11 (28)

10. Diuretic use, n (%): 2 (5)

11. Serum urate, mmol/l, mean (SD): 0.44 (0.11)
12. Tophaceous gout, n (%): 8 (20%)

13. Serum creatinine, µmol/l, mean (SD): 91 (18)

SMP group (n = 40):

1. Males, n (%): 36 (90)

2. Mean age, years (SD): 56 (12)

3. Caucasian ethnicity, n (%): 28 (70)

4. Number of self reported flares in preceding 4 months, mean (SD): 4.5 (2.3)

5. Number of gout flares in baseline month, mean (SD): 1.1 (1.4)

6. Allopurinol use, n (%): 22 (55)

7. Colchicine use, n (%): 7 (18)

8. Prednisone use, n (%): 8 (20)

9. NSAID use, n (%): 10 (25)

10. Diuretic use, n (%): 1 (2.5)

11. Serum urate, mmol/l, mean (SD): 0.41 (0.09)
12. Tophaceous gout, n (%): 17 (43)

13. Serum creatinine, µmol/l, mean (SD): 91 (19)

SMP/GMP/G600 (n = 40):

Dalbeth 2012 *(Continued)*

	1. Males, n (%): 35 (88) 2. Mean age, years (SD): 56 (13) 3. Caucasian ethnicity, n (%): 22 (55) 4. Number of self reported flares in preceding 4 months, mean (SD): 5.1 (9.6) 5. Number of gout flares in baseline month, mean (SD): 1.8 (2.4) 6. Allopurinol use, n (%): 22 (55) 7. Colchicine use, n (%): 13 (33) 8. Prednisone use, n (%): 4 (10) 9. NSAID use, n (%): 11 (28) 10. Diuretic use, n (%): 8 (20) 11. Serum urate, mmol/l, mean (SD): 0.42 (0.11) 12. Tophaceous gout, n (%): 10 (25) 13. Serum creatinine, µmol/l, mean (SD): 93 (20)
Interventions	Intervention 1: lactose powder active control Intervention 2: skim milk powder (SMP) active control Intervention 3: SMP enriched with GMP and G600 (1.5 g GMP protein (10% total protein) and 0.525 g G600 (3.5% of total protein weight))
Outcomes	Outcome assessments at 1, 2 and 3 months: Primary endpoint: change in frequency of gout flares Secondary endpoints: 1. Change in swollen joint count (/66) 2. Change in tender joint count (/68) 3. Pain (10-point Likert), (scored 0 to 10) where 0 (no pain) and 10 (severe pain) 4. Patient global assessment (0 to 100), where 0 (very well) and 100 (very poor) 5. C-reactive protein (CRP) (mg/l) 6. Serum uric acid concentration (mmol/l) 7. Fractional excretion of UA (%) 8. Health Assessment Questionnaire (HAQ-II), 10-item questionnaire, each item scored from 0 (without any difficulty) to 3 (unable to perform). Sum of the scores of each questionnaire item is divided by the number of questions answered to obtain a value between 0 (minimal loss of function) and 3 (completely disabled) 9. Open-ended enquiry to elicit adverse events
Notes	Unpublished data (HAQ results) sought and received from the study author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized using a random block randomization algorithm"

Dalbeth 2012 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote: "Participants and study staff were blinded to treatment allocation throughout the study..." Comment: insufficient details provided of the actual method of allocation concealment to intervention. No further information obtained in spite of attempts to contact the study author.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The products were dry-blended and packed into identical, custom-made aluminium foil sachets...Each intervention was a cream-coloured powder administered daily as a 250 ml vanilla flavoured shake"
Blinding of outcome assessment (detection bias) Patient assessed outcomes	Low risk	1. Gout flare frequency 2. Patient global assessment 3. Health assessment questionnaire (HAQ-II)
Blinding of outcome assessment (detection bias) Examiner assessed outcomes	Unclear risk	1. Tender joint count 2. Swollen joint count 3. Adverse events Quote: "Study staff were blinded to treatment allocation throughout the study..." Comment: although not explicitly stated, it was implied from the aforementioned statement that outcome assessors were blinded. No further clarification was available despite attempts to contact the study author.
Blinding of outcome assessment (detection bias) Laboratory assessed outcomes	Unclear risk	1. Serum urate concentration 2. Fractional excretion of uric acid 3. C-reactive protein Quote: "Study staff were blinded to treatment allocation throughout the study..." Comment: although not explicitly stated, it was implied from the aforementioned statement that outcome assessors were blinded. No further clarification was available despite attempts to contact the study author.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Of the 120 patients enrolled in the study, two patients discontinued due to adverse events, eight were lost to follow-up, and eight continued in the study without taking the milk products after experiencing an adverse event (intention to treat). One hundred and two patients completed the study as per protocol." Comment: distribution of drop-outs between groups not specified. No further clarification was available despite attempts to contact the study author.
Selective reporting (reporting bias)	Unclear risk	Comment: all prespecified outcomes reported. There was selective reporting of a post hoc comparison between SMP/GMP/G600 and lactose powder control on change in gout flare frequency and lowering of diastolic BP.
Other bias	Unclear risk	Quote: "The study was registered as a clinical trial with the Australian New Zealand Clinical Trials Registry (ACTRN12609000479202)". COI: "This work was funded by LactoPharma (a joint venture between Fonterra Ltd, Fonterra R&D Ltd and Auckland UniServices Ltd) and the New Zealand Government Foundation for Research Science and Technology. Barbara Kuhn-Sherlock, Alastair MacGibbon and Kate Palmano are employees of Fonterra Co-operative Group Ltd. Alastair MacGibbon, Nicola Dalbeth and Kate Palmano are named inventors on a patent application related to milk products and gout."

BP: blood pressure

COI: conflict of interest
NSAID: non-steroidal anti-inflammatory drug
SD: standard deviation
SMP: skim milk powder
UA: uric acid

Characteristics of studies awaiting assessment *[ordered by study ID]*

Zeng 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting translation

Zhao 2009

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting translation

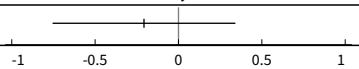
DATA AND ANALYSES

Comparison 1. SMP (GMP/G600) versus control (SMP/lactose)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of gout flares per month, after 3 months SMP (GMP/G600) versus control (SMP/lactose)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2 Physical Function	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3 Participant withdrawals due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 SMP (GMP/G600) versus control (SMP/lactose), Outcome 1 Number of gout flares per month, after 3 months SMP (GMP/G600) versus control (SMP/lactose).

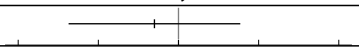
Study or subgroup	SMP (GMP/G600)		Control (SMP/lactose)		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Dalbeth 2012	40	0.5 (1.5)	80	0.7 (1.3)		0%	-0.21[-0.76,0.34]



Favours SMP (GMP/G600) — Favours control

Analysis 1.2. Comparison 1 SMP (GMP/G600) versus control (SMP/lactose), Outcome 2 Physical Function.

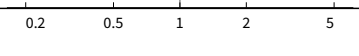
Study or subgroup	SMP (GMP/G600)		Control (SMP/lactose)		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Dalbeth 2012	35	0.1 (0.2)	69	0.1 (0.3)		0%	-0.03[-0.14,0.08]



Favours GMP/G600 — Favours SMP/Lactose

Analysis 1.3. Comparison 1 SMP (GMP/G600) versus control (SMP/lactose), Outcome 3 Participant withdrawals due to adverse events.

Study or subgroup	SMP (GMP/G600)	Control (SMP/lactose)	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Dalbeth 2012	7/40	11/80		0%	1.27[0.53,3.03]



Favours GMP/G600 — Favours SMP/Lactose

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Gout explode all trees

#2 gout*:ti,ab

#3 (#1 OR #2)

#4 MeSH descriptor Ethanol explode all trees

#5 ethanol:ti,ab

#6 MeSH descriptor Alcohol-Related Disorders explode all trees

#7 MeSH descriptor Alcohol Drinking, this term only

#8 alcohol*:ti,ab

#9 MeSH descriptor Exercise explode all trees

#10 MeSH descriptor Exercise Therapy explode all trees

#11 MeSH descriptor Exercise Movement Techniques explode all trees

#12 MeSH descriptor Physical Education and Training explode all trees

#13 MeSH descriptor Physical Fitness, this term only

#14 MeSH descriptor Physical Exertion, this term only

#15 MeSH descriptor Sports explode all trees

#16 exercis*:ti,ab

#17 sport*:ti,ab

#18 (physical* next (fit* or exert* or activ*)):ti,ab

#19 (run* or jog* or walk*):ti,ab

#20 (swim* or cycl* or bicycl*):ti,ab

#21 train*:ti,ab

#22 kinesi?therap*:ti,ab

#23 ((weight or muscle*) next (strength* or resistance)):ti,ab

#24 endurance:ti,ab

#25 MeSH descriptor Tobacco explode all trees

#26 MeSH descriptor Tobacco Use Disorder, this term only

#27 MeSH descriptor Tobacco Use Cessation explode all trees

#28 MeSH descriptor Tobacco Smoke Pollution explode all trees

#29 MeSH descriptor Nicotine, this term only

#30 smok*:ti,ab

#31 (cigarette* or cigar* or pipe*):ti,ab

#32 (#4 OR #5 OR #6 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31)

#33 MeSH descriptor Weight Loss explode all trees

#34 weight loss:ti,ab

#35 (weight near/2 (lo* or reduc* or eliminat*)):ti,ab

#36 ((body mass index or bmi) near/3 (los* or reduc* or decreas* or low*)):ti,ab

#37 (Waist circumference near/2 (reduc* or low* or small*)):ti,ab

#38 (Waist size near/2 (reduc* or low* or small*)):ti,ab

#39 energy next restrict*:ti,ab

#40 (calor* near/2 (restrict* or reduc* or low*)):ti,ab

#41 MeSH descriptor Anti-Obesity Agents explode all trees

#42 (appetite near/2 suppress*):ti,ab

#43 orlistat:ti,ab

#44 xenical:ti,ab

#45 alli:ti,ab

#46 tetrahydrolipstatin:ti,ab

#47 phentermine:ti,ab

#48 phenyl-tertiary-butylamine:ti,ab

#49 Ionamin:ti,ab

#50 adipex-P:ti,ab

#51 anoxine-AM:ti,ab

#52 duromine:ti,ab

#53 metermine:ti,ab

#54 mirapront:ti,ab

#55 obephen:ti,ab

#56 obestin-30:ti,ab

#57 phentremene:ti,ab

#58 phentrol:ti,ab

#59 phenterex:ti,ab

#60 phentromin:ti,ab

#61 "pro-fast SA":ti,ab

#62 redusa:ti,ab

#63 panbesy:ti,ab

#64 "phentermine trenker":ti,ab

#65 Obenix:ti,ab

#66 Oby-trim:ti,ab

#67 Teramine:ti,ab

#68 Zantryl:ti,ab

#69 Sinpet:ti,ab

#70 Supremin:ti,ab

#71 Umine:ti,ab

#72 Weltmine:ti,ab

#73 Aplenzin:ti,ab

#74 (#33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #69 OR #70 OR #71 OR #72 OR #73)

#75 MeSH descriptor Diet explode all trees

#76 diet*:ti,ab

#77 MeSH descriptor Nutrition Therapy explode all trees

#78 (lacto-vegetarian* or lacto vegetarian* or vegetarian* or non-vegetarian*):ti,ab

#79 non near/2 vegetarian*:ti,ab

#80 vegan*:ti,ab

#81 (Cretan or Mediterranean):ti,ab

#82 MeSH descriptor Fasting, this term only

#83 fast*:ti,ab

#84 (protein near/2 (restrict* or reduc* or low* or elim*)):ti,ab

#85 (purine near/2 (restrict* or reduc* or low* or elim*)):ti,ab

#86 (fat near/2 (restrict* or reduc* or low* or elim)):ti,ab

#87 (triglyceride near/2 (restrict* or reduc* or low* or elim*)):ti,ab

#88 (cholesterol near/2 (restrict* or reduc* or low* or elim*)):ti,ab

#89 (diet near/3 (reduc* or low* or restrict* or elim*)):ti,ab

#90 (#75 OR #76 OR #77 OR #78 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89)

#91 MeSH descriptor Dairy Products explode all trees

#92 (milk or cheese* or yog?urt or dairy):ti,ab

#93 MeSH descriptor Milk, this term only

#94 MeSH descriptor Cultured Milk Products, this term only

#95 (#91 OR #92 OR #93 OR #94)

#96 MeSH descriptor Sucrose explode all trees

#97 MeSH descriptor Fructose, this term only

#98 (sucrose* or lactose* or glucose* or fructose* or glycerine* or lycerine* or dextrose* or aspartame* or polycose* or sacchar* or sugar*):ti,ab

#99 (sweet* near/6 (solution* or tast*)):ti,ab

#100 (Diet* near/3 (drink* or beverage*)):ti,ab

#101 (soft near/2 (drink* or beverage*)):ti,ab

#102 (soda or sodas):ti,ab

#103 (#96 OR #97 OR #98 OR 99 OR #100 OR #101 OR #102)

#104 MeSH descriptor Coffee, this term only

#105 MeSH descriptor Caffeine, this term only

#106 (coffee or caffiene or caffeinated or decaffeinated):ti,ab

#107 (#104 OR #105 OR #106)

#108 MeSH descriptor Life Style explode all trees

#109 (life near/2 (style* or change$*or event*)):ti,ab

#110 lifestyle*:ti,ab

#111 MeSH descriptor Social Support, this term only

#112 "social support":ti,ab

#113 MeSH descriptor Relaxation explode all trees

#114 MeSH descriptor Relaxation Therapy, this term only

#115 relax*:ti,ab

#116 MeSH descriptor Self Efficacy, this term only

#117 (self next (efficac* or help or manag* or care)):ti,ab

#118 MeSH descriptor Health Promotion explode all trees

#119 MeSH descriptor Health Education explode all trees

#120 (health next (promot* or educat*)):ti,ab

#121 (motivat* next (therap* or interview*)):ti,ab

#122 (#108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #115 OR #116 OR #117 OR #118 OR #119 OR #120 OR #121)

#123 (#32 OR #74 OR #90 OR #95 OR #107 OR #122)

#124 (#3 AND #123)

Appendix 2. MEDLINE search strategy

1. exp gout/

2. gout$.tw.

3. 1 or 2

4. exp life style/

5. (life adj2 (style$ or change$ or event$)).tw.

6. lifestyle$.tw.

7. social support/

8. social support.tw.

9. exp relaxation/ or relaxation therapy/

10. relax$.tw.

11. self efficacy/

12. (self adj (efficac$ or help or manag$ or care)).tw.

13. exp health promotion/

14. exp health education/

15. (health adj (promot$ or educat$)).tw.

16. (motivat$ adj (therap$ or interview$)).tw.

17. or/4-16

18. exp Weight Loss/

19. weight loss.tw.

20. (weight adj2 (lo$ or reduc$ or eliminat$)).tw.

21. ((body mass index or bmi) adj3 (los$ or reduc$ or decreas$ or low$)).tw.

22. (Waist circumference adj2 (reduc$ or low$ or small$)).tw.

23. (Waist size adj2 (reduc$ or low$ or small$)).tw.

24. energy restrict$.tw.

25. (calor$ adj2 (restrict$ or reduc$ or low$)).tw.

26. exp Anti-Obesity Agents/

27. (appetite adj2 suppress$).tw.

28. orlistat.tw.

29. xenical.tw.

30. alli.tw.

31. tetrahydrolipstatin.tw.

32. phentermine.tw.

33. phenyl-tertiary-butylamine.tw.

34. Ionamin.tw.

35. adipex-P.tw.

36. anoxine-AM.tw.

37. duromine.tw.

38. metermine.tw.

39. mirapront.tw.

40. obephen.tw.

41. obestin-30.tw.

42. phentremene.tw.

43. phentrol.tw.

44. phenterex.tw.

45. phentromin.tw.

46. pro-fast SA.tw.

47. redusa.tw.

48. panbesy.tw.

49. phentermine trenker.tw.

50. Obenix.tw.

51. Oby-trim.tw.

52. Teramine.tw.

53. Zantryl.tw.

54. Sinpet.tw.

55. Supremin.tw.

56. Umine.tw.

57. Weltmine.tw.

58. Aplenzin.tw.

59. or/18-58

60. exp diet/

61. diet$.tw.

62. exp Nutrition Therapy/

63. (lacto-vegetarian$ or lacto vegetarian$ or vegetarian$ or non-vegetarian$).tw.

64. (non adj2 vegetarian$).tw.

65. vegan$.tw.

66. (Cretan or Mediterranean).tw.

67. Fasting/

68. fast$.tw.

69. (protein adj2 (restrict$ or reduc$ or low$ or elim$)).tw.

70. (purine adj2 (restrict$ or reduc$ or low$ or elim$)).tw.

71. (fat adj2 (restrict$ or reduc$ or low$ or elim$)).tw.

72. (triglyceride adj2 (restrict$ or reduc$ or low$ or elim$)).tw.

73. (cholesterol adj2 (restrict$ or reduc$ or low$ or elim$)).tw.

74. (diet adj3 (reduc$ or low$ or restrict$ or elim$)).tw.

75. or/60-74

76. exp Dairy Products/

77. (milk or cheese$ or yog?urt or dairy).tw.

78. milk/ or cultured milk products/

79. or/76-78

80. exp Sucrose/

81. Fructose/

82. (sucrose$ or lactose$ or glucose$ or fructose$ or glycerine$ or lycerine$ or dextrose$ or aspartame$ or polycose$ or sacchar$ or sugar $).tw.

83. (sweet$ adj6 (solution$ or tast$)).tw.

84. (Diet$ adj3 (drink$ or beverage$)).tw.

85. (soft adj2 (drink$ or beverage$)).tw.

86. (sugar adj2 free adj2 (drink$ or beverage$)).tw.

87. (soda or sodas).tw.

88. or/80-87

89. Coffee/

90. Caffeine/

91. (coffee or caffiene or caffeinated or decaffeinated).tw.

92. or/89-91

93. exp Ethanol/

94. ethanol.tw.

95. exp Alcohol-Related Disorders/

96. Alcohol Drinking/

97. alcohol$.tw.

98. or/93-97

99. exp exercise/

100. exp Exercise Therapy/

101. exp Exercise Movement Techniques/

102. exp "Physical Education and Training"/

103. Physical Fitness/

104. Physical Exertion/

105. exp sports/

106. exercis$.tw.

107. sport$.tw.

108. (physical$ adj (fit$ or exert$ or activ$)).tw.

109. (run$ or jog$ or walk$).tw.

110. (swim$ or cycl$ or bicycl$).tw.

111. train$.tw.

112. kinesi?therap$.tw.

113. ((weight or muscle$) adj (strength$ or resistance)).tw.

114. endurance$.tw.

115. or/99-114

116. exp Tobacco/

117. "Tobacco Use Disorder"/

118. exp "Tobacco Use Cessation"/

119. Tobacco Smoke Pollution/

120. Nicotine/

121. smok$.tw.

122. (cigarette$ or cigar$ or pipe$).tw.

123. Nicotinic Agonists/

124. (nicotine adj (replacement or patch$ or gum or nasal)).tw.

125. nrt.tw.

126. nicorette.tw.

127. Nicotrol.tw.

128. Nicoderm$.tw.

129. Habitrol.tw.

130. Bupropion/

131. Bupropion.tw.

132. Amfebutamone.tw.

133. Aplenzin.tw.

134. Budeprion.tw.

135. Buproban.tw.

136. Butrew.tw.

137. Buxon.tw.

138. champix.tw.

139. Clorprax.tw.

140. Dosier.tw.

141. Elontril.tw.

142. Mondrian.tw.

143. Nicotex.tw.

144. Prexaton.tw.

145. Quomem.tw.

146. Voxra.tw.

147. Wellbutrin.tw.

148. Zetron.tw.

149. Zyban.tw.

150. Zyntabac.tw.

151. varenicline.tw.

152. exp hypnosis/

153. hypno$.tw.

154. exp counseling/

155. counsel$.tw.

156. or/116-155

157. or/17,59,75,79,88,92,98,115,156

158. 3 and 157

159. randomized controlled trial.pt.

160. controlled clinical trial.pt.

161. randomized.ab.

162. placebo.ab.

163. drug therapy.fs.

164. randomly.ab.

165. trial.ab.

166. groups.ab.

167. or/159-166

168. (animals not (humans and animals)).sh.

169. 167 not 168

170. 158 and 169

Appendix 3. EMBASE search strategy

1. exp gout/

2. gout$.tw.

3. 1 or 2

4. exp life style/

5. Lifestyle modification/

6. (life adj2 (style$ or change$ or event$)).tw.

7. lifestyle$.tw.

8. Social support/

9. social support.tw.

10. Relaxation training/

11. relax$.tw.

12. Self concept/ or exp self care/

13. (self adj (efficac$ or help or manag$ or care)).tw.

14. Health promotion/

15. exp health education/

16. (health adj (promot$ or educat$)).tw.

17. (motivat$ adj (therap$ or interview$)).tw.

18. 4 or 17

19. weight reduction/

20. (weight adj2 (lo$ or reduc$ or eliminat$)).tw.

21. ((body mass index or bmi) adj3 (los$ or reduc$ or decreas$ or low$)).tw.

22. (Waist circumference adj2 (reduc$ or low$ or small$)).tw.

23. (Waist size adj2 (reduc$ or low$ or small$)).tw.

24. energy restrict$.tw.

25. (calor$ adj2 (restrict$ or reduc$ or low$)).tw.

26. antiobesity agent/

27. (appetite adj2 suppress$).tw.

28. orlistat.tw.

29. xenical.tw.

30. alli.tw.

31. tetrahydrolipstatin.tw.

32. phentermine.tw.

33. phenyl-tertiary-butylamine.tw.

34. Ionamin.tw.

35. adipex-P.tw.

36. anoxine-AM.tw.

37. duromine.tw.

38. metermine.tw.

39. mirapront.tw.

40. obephen.tw.

41. obestin-30.tw.

42. phentremene.tw.

43. phentrol.tw.

44. phenterex.tw.

45. phentromin.tw.

46. pro-fast SA.tw.

47. redusa.tw.

48. panbesy.tw.

49. phentermine trenker.tw.

50. Obenix.tw.

51. Oby-trim.tw.

52. Teramine.tw.

53. Zantryl.tw.

54. Sinpet.tw.

55. Supremin.tw.

56. Umine.tw.

57. Weltmine.tw.

58. amfebutamone/

59. Aplenzin.tw.

60. Zyban.tw.

61. or/19-60

62. exp diet/

63. diet$.tw.

64. exp diet therapy/

65. (lacto-vegetarian$ or lacto vegetarian$ or vegetarian$ or non-vegetarian$).tw.

66. (non adj2 vegetarian$).tw.

67. vegan$.tw.

68. (Cretan or Mediterranean).tw.

69. fast$.tw.

70. (protein adj2 (restrict$ or reduc$ or low$ or elim$)).tw.

71. (purine adj2 (restrict$ or reduc$ or low$ or elim$)).tw.

72. (fat adj2 (restrict$ or reduc$ or low$ or elim$)).tw.

73. (triglyceride adj2 (restrict$ or reduc$ or low$ or elim$)).tw.

74. (cholesterol adj2 (restrict$ or reduc$ or low$ or elim$)).tw.

75. or/62-73

76. exp dairy product/

77. (milk or cheese$ or yog?urt or dairy).tw.

78. milk/

79. or/76-78

80. sucrose/

81. fructose/

82. (sucrose$ or lactose$ or glucose$ or fructose$ or glycerine$ or lycerine$ or dextrose$ or aspartame$ or polycose$ or sacchar$ or sugar $).tw.

83. (sweet$ adj6 (solution$ or tast$)).tw.

84. (Diet$ adj3 (drink$ or beverage$)).tw.

85. (soft adj2 (drink or beverage)).tw.

86. (sugar adj2 free adj2 (drink$ or beverage$)).tw.

87. (soda or sodas).tw.

88. or/80-87

89. coffee/

90. caffeine/

91. (coffee or caffiene or caffeinated or decaffeinated).tw.

92. or/89-91

93. alcohol/

94. ethanol.tw.

95. alcoholism/

96. drinking behavior/

97. alcohol$.tw.

98. or/93-97

99. exp exercise/

100. exp kinesiotherapy/

101. physical education/

102. fitness/

103. exp sports/

104. exercis$.tw.

105. sport$.tw.

106. (physical$ adj (fit$ or exert$ or activ$)).tw.

107. (run$ or jog$ or walk$).tw.

108. (swim$ or cycl$ or bicycl$).tw.

109. train$.tw.

110. kinesi?therap$.tw.

111. ((weight or muscle$) adj (strength$ or resistance)).tw.

112. endurance.tw.

113. or/99-112

114. tobacco/

115. tobacco dependence/

116. smoking cessation/

117. exp "smoking and smoking related phenomena"/

118. nicotine/

119. smok$.tw.

120. (cigarette$ or cigar$ or pipe$).tw.

121. nicotine replacement therapy/

122. (nicotine adj (replacement or patch$ or gum or nasal)).tw.

123. nrt.tw.

124. nicorette.tw.

125. Nicotrol.tw.

126. Nicoderm$.tw.

127. Habitrol.tw.

128. amfebutamone/

129. Bupropion.tw.

130. Amfebutamone.tw.

131. Aplenzin.tw.

132. Budeprion.tw.

133. Buproban.tw.

134. Butrew.tw.

135. Buxon.tw.

136. champix.tw.

137. Clorprax.tw.

138. Dosier.tw.

139. Elontril.tw.

140. Mondrian.tw.

141. Nicotex.tw.

142. Prexaton.tw.

143. Quomem.tw.

144. Voxra.tw.

145. Wellbutrin.tw.

146. Zetron.tw.

147. Zyban.tw.

148. Zyntabac.tw.

149. varenicline.tw.

150. hypnosis/

151. hypno$.tw.

152. exp counseling/

153. counsel$.tw.

154. or/114-153

155. or/18,61,75,79,88,92,98,113,154

156. 3 and 155

157. (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.

158. RETRACTED ARTICLE/

159. 157 or 158

160. (animal$ not human$).sh,hw.

161. (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/

162. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/

163. 159 not (160 or 161 or 162)

164. 156 and 163

WHAT'S NEW

Date	Event	Description
24 September 2019	Amended	Typo in the plain language summary corrected and text clarified

HISTORY

Protocol first published: Issue 8, 2012
Review first published: Issue 5, 2013

Date	Event	Description
18 December 2013	Amended	Added physical function data, provided by the trial author

CONTRIBUTIONS OF AUTHORS

JM wrote the current version of the review. RB, CE and MS provided comments and suggestions on draft versions of the review, and all authors approved the final version.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- The Royal Melbourne Hospital, Australia.

  In kind support
- Monash University, Australia.

  In kind support
- Cabrini Hospital, Australia.

  In kind support
- Southampton General Hospital, UK.

  In kind support

External sources

- No external sources of support, Other.

INDEX TERMS

Medical Subject Headings (MeSH)

*Life Style; *Milk; Caseins [*therapeutic use]; Chronic Disease; Gout [*diet therapy]; Lactose [*therapeutic use]; Peptide Fragments [*therapeutic use]; Powders; Randomized Controlled Trials as Topic

MeSH check words

Animals; Humans; Middle Aged